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**Title: Glycaemic (HbA1c) variability and mortality in older people (age  $\geq 70$  years) with diabetes mellitus: a retrospective cohort study.**

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## Research in context

### *Evidence before this study*

We have searched PubMed and Scopus from 1990-2017, to identify relevant studies that contain terms for older people; all-cause mortality; glycaemic control; glycaemic variability (with synonyms). We also identified current international guidelines for older people. Overall, the data on optimal glycaemic targets for older people are scant, particularly from prospective studies. In terms of the association between glycaemic control and mortality in older populations the findings have suggested a 'J' shaped distribution in that relationship, although the point at which a significant mortality hazard is observed at the lower end of the glycaemic range has varied between studies. In terms of glycaemic variability, it has been identified that longer term variations in glycaemic control are associated with mortality risk. However, these analyses have not been graduated for magnitude or direction of variability. In addition, previous analyses have not considered the impact of low HbA1c levels, which are associated with mortality risk independent of diabetes intervention.

### *Added value of this study*

In this large population study we are the first group to consider both glycaemic control and glycaemic variability together. We have also employed a new metric for variability which considers exposure to clinically significant changes in glycaemic control. This metric enabled us to assess the direction of change as well as the overall variability. Integrating glycaemic control and variability in our modelling enabled us to consider the importance of stability as a potential factor in understanding the mortality hazard in this population. Additional nuances to our analysis include: consideration of low HbA1c values; higher levels of granularity compared to previous studies in terms of glycaemic thresholds, with 0.5% (5.5mmol/l) HbA1c increments; consideration of gender differences; and the distinction between those who develop diabetes in midlife and those who develop it in older age.

### *Implications of all the available evidence*

Our data suggest that we may need to rethink how we consider glycaemic targets in the older diabetes population, in a number of ways: firstly, that variability expresses significant hazard in older people; secondly, that variability may be independent of diabetes therapies and may be related to other factors related to aging; thirdly, stability seems to attenuate hazard in medium to higher ranges of glycaemic control; and finally, there may be some important gender differences in relation to glycaemic control and hazard which are not considered in current guidelines. Therefore, while we recognise that observational data can often raise more questions than answers; we would advocate that we reconsider glycaemic control not simply as a target to direct therapeutic management, but as an important piece of information in relation to assessing individual risk. Perhaps in the past we have been too polarised in our view of glycaemia as purely indicative of optimal control, rather than as a potential important biometric in assessing older people with diabetes. There is still much we do not know and this study did not include the tools necessary to expose important measures of aging: such as frailty; physical activity; and nutrition. Clearly, we now need some translational studies both to consider how we might consider HbA1c values as a metric in older people and to inform more optimal approaches to achieving a safe and stable glucose environment.

## Summary

**Background:** Glycaemic targets for older people have been revised in recent years over concern that more stringent levels are associated with elevated mortality hazard. In this study, we explore this association considering glycaemic control and variability.

**Methods:** A 5 year retrospective cohort study using a large primary care dataset examining glycaemic control and variability exposures on all-cause mortality. The cohort comprised 54,803 patients with Type 1 and 2 diabetes aged  $\geq 70$  years, mean age 78.3(SD5.7) and 51% were female. Glycaemic control(HbA1c) was assessed in three models using: a baseline mean; whole follow-up period mean; and time-varying yearly updated mean. Glycaemic variation was assessed using an instability metric based on number of changes in  $HbA1c \geq 0.5\%$  (5.5mmol/mol), scored low to high, 0-100.

**Findings:** There were 17,680 deaths during the observation period, the mortality rate was 77 per 1000 person years. The data showed a 'J' shaped distribution for mortality hazard with significant elevations with HbA1c values  $>8\%$  (64mmol/mol) and  $<6\%$  (42mmol/mol). Survival diminished markedly with increasing instability in all models. For the whole period HbA1c measure the hazard ratios in patients with the highest instability metric ( $>80-100$ ) ( $n=1,227$ ) were 2.47 for females and 2.21 for males. Fitting the glycaemic control models with the instability metric softened the hazard distribution with significant hazard only being observed with HbA1c values  $>10\%$  (86mmol/mol) in males and  $>9.5\%$  (80mmol/mol) in females.

**Interpretation:** The data suggests that glycaemic variability may be an important factor in understanding mortality hazard in older people with diabetes.

**Funding:** King's College London, Diabetes Frail

## INTRODUCTION

A key challenge for clinicians in enhancing diabetes care in older people is the need to address the continuing uncertainty about the thresholds for benefit and hazard in relation to glycaemic control.<sup>1</sup> Recent observational studies,<sup>2-4</sup> have reported a 'J' shaped distributions for mortality and glycaemic control, with mortality being associated not only with elevated glycated haemoglobin (HbA1c) but also more stringent levels ( $\text{HbA1c} \leq 7.0\%$  ( $\leq 53\text{mmol/mol}$ )). These data, together with the varied outcomes of recent trials assessing intensive glucose lowering in patients with type 2 diabetes,<sup>5-8</sup> have led to an emphasis on individualised, less stringent, glycaemic targets for older people in current guidelines.<sup>9,10</sup> However, while the move toward a more individualised approach is progressive, we need a better understanding of the hazard conferred by glycaemic exposure to direct clinical decisions and prevent either excess or inadequate utilisation of hypoglycaemic therapies.

In our analysis, we introduce some novel considerations in assessing the relationship between mortality risk in older people and glycaemia, to extend the observations of previous studies. In addition to assessing average glycaemic control we have considered the relationship between the degree of variability in glycaemic control (HbA1c) over time with mortality. A recent meta-analysis reported increased hazard for diabetes complications and mortality with higher levels of glycaemic variation.<sup>11</sup> Our analysis has also attempted to address some of the heterogeneity and complexity within the older population, by considering factors such as diabetes duration, gender differences, hypoglycaemic therapies, comorbidities and polypharmacy. Having reviewed the previous studies we further refined our analysis, by: considering the impact of very low HbA1c values ( $<5\%$ ,  $31\text{mmol/mol}$ ), which may be associated with elevated mortality hazard independent of diabetes;<sup>12,13</sup> and introducing more granularity in the exposure thresholds for glycaemic targets, to provide more precise estimations of the hazard distribution.

## METHODS

### Study design and subjects

We conducted a 5 year retrospective cohort study examining the relationship between glycaemic control and all-cause mortality in patients with diabetes, considering both mean glycaemic control and variability. We also assessed: treatment modalities (oral hypoglycaemic agents(OHA) and insulin); other metabolic targets (blood pressure and lipids); comorbidities; polypharmacy; and sociodemographic factors. The analysis used the Health Innovation Network(THIN) primary care based dataset, which is derived from 587 UK primary care practices and is constructed using standardised READ codes. THIN has been validated against normative data for mortality and morbidities.<sup>14</sup> We included all patients aged  $\geq 70$  years on the 1<sup>st</sup> January 2007 with a recorded diagnosis of diabetes  $\geq 6$  months ( $n=54,803$ ) from the dataset using a previously developed algorithm.<sup>15</sup> The sample includes patients with both Type 1 and Type 2 diabetes as the coding of diabetes type in primary care is unreliable, it can be assumed that at least 90% were Type 2.

### Outcome and exposure

The primary outcome was time to all-cause mortality. Our primary exposure variables were mean glycated haemoglobin and glycaemic variability. We considered the following exposure measures in three models:

- I. Mean of the annual mean HbA1C for 2003, 2004, 2005 and 2006;
- II. Mean of the annual mean HbA1C from 2003 until the year before the person died or last year of follow-up.

### III. Updated annual mean from 2003 onwards (used in a time-varying model)

If mean HbA1c was missing for a given year it was replaced with the mean of the non-missing annual means so if a person was still alive in 2008, and mean HbA1c was missing for 2004 and 2006 the cumulative mean was the mean of the annual means for 2003, 2005 and 2007.

Models I and II indicate longer term effects of glycaemic control, whereas Model III associates more to short-term effects. These exposure variables were categorised by 0.5%(1.5mmol/mol)HbA1c increments, except for the outlying low and high values (3.0%(9mmol/mol)-<6.0%(42mmol/mol), and >10%(86mmol/mol)) as the number of patients at these thresholds was smaller. We evaluated data completeness, the percentage of people with >1 valid HbA1c measurements per annum increased from 55% in 2003 to 76% in 2005, remaining around this level thereafter.

To assess variability in HbA1c we counted the number of times the current and previous readings differed by  $\geq 0.5\%$  (5.5mmol/mol), divided this number by the number of comparisons and then multiplied by 100. For example, if a person had the following sequence of HbA1c values: 6.7, 7.0, 7.8, 7.4, 8.0, 7.9 their count would be two and the metric would equal 40 (i.e.  $100 \times 2/5$ ). The metric can therefore range from 0(low) to 100(high). For analysis purposes this metric was grouped into 0-20, 21-40, 41-60, 61-80 and 81-100. We used increments of 0.5%(5.5mmol/mol) in HbA1c as an accepted indicator of a clinically significant differences in glucose exposure. The count was also split into those that were directionally positive or negative (their sum equals the total count). These two counts were divided by the number of comparisons and multiplied by 100, as above, to produce two additional metrics for sensitivity analysis purposes. We also considered the standard deviation of the annual mean HbA1c as an additional measure of variability exposure, grouped into quintiles and the slope of mean HbA1c over time as an alternative direction measure.

The risk adjusters were: age; ethnicity; deprivation(Townsend); diabetes duration; body mass index(BMI); smoking-status; hypertension; LDL cholesterol, chronic kidney disease(CKD) stage, amputation; laser photocoagulation; co-morbidity; polypharmacy; and diabetes therapies prescribed in the three months before baseline(1<sup>st</sup> January 2007). Ethnicity and deprivation(Townsend scores) were estimated using postcode level variables linked to a person's address and organised by quintiles with 1 being least diverse/deprived and 5 being most diverse/deprived. To assess the overall comorbidity load a primary care equivalent of the Charlson Index<sup>16</sup> and a count of 12 comorbidities(CKD, heart failure, atrial fibrillation, hypertension, peripheral arterial disease(PAD), stroke, cancer, dementia, depression, asthma, COPD and hypothyroidism) were used. Polypharmacy was categorised into four ordinal groups (0-2,3-4,5-6, $\geq 7$  medicines) based on a count of therapies (defined using British National Formulary(BNF) categorisation) received continuously for >6 months. Duration of diabetes in years at baseline was categorised into four groups (<3, 3 - <5, 5- <10,  $\geq 10$ ). When data for a variable was missing an unknown category was added.

Diabetes therapies were included in the model and were categorised using the BNF as follows: sulphonylureas(SUs); biguanides; thiazolidinedione(TZD); acarbose or guar gum; and insulin. Newer agents such as incretin therapies and selective glucose reuptake inhibitors were not included as exposure to these therapies was negligible during the study period, together with repaglinide which is rarely used in the UK.

### Statistical analysis

Cox regression was used to model time to death and calculate the unadjusted and adjusted hazard ratios for HbA1c group (reference category 7.0(53mmol/mol)-<7.5%(58mmol/mol)) and instability metric

quintiles (reference category 0-20) in models I-III. An additional fully adjusted model for the HbA1c groups was projected adjusting for instability. The SAS procedure PHREG, with robust sandwich estimates<sup>17</sup> to correct for intra-cluster dependence (Models I-II: general practices; Model III: general practices and people), was used to fit the non-time varying(I and II) and time varying(III) models. There was some evidence of collinearity amongst the independent variables. A small number had variance inflation factors(VIF) >10. These were mainly associated with CKD. However, we retained CKD because of its importance in predicting mortality. Models were fitted by gender to the 70-74, 75-79, 80-84, 85 and over and 70 and over age-groups.

### Sensitivity Analysis

Sensitivity analyses were undertaken to consider the impact of: replacing the Charlson index and comorbidity count with individual comorbidities; standard deviation of mean HbA1c as alternative to the stability metric; direction of movement in glycaemic change based on the impact of either increases or decreases in the stability metric of 20% or more; and linear slope estimated from individual person level regressions of mean annual HbA1c on year; very low HbA1c values (removal of outlying HbA1c values <5.0%(31mmol/mol)); BMI and low HbA1c (to assess whether a low HbA1c and a low BMI conflated mortality risk); and diabetes duration (independent hazard assessment in those diagnosed <65 years of age and those diagnosed ≥65 years).

All variables in Models I-III using the Charlson index and number of comorbidities as adjusters were tested individually for non-proportionality. This resulted in 630 and 660 tests for models fitting HbA1c level, and HbA1c level and the instability metric respectively. Due to the large number of tests only those achieving  $p < 0.001$  are referred to in the results. The analysis was internally funded by King's College London, with no influence on the conduct or interpretation of the analysis.

## RESULTS

The cohort was comprised of 54,803 people, with an equal gender divide (Table 1). The mean age was 79.0(SD 6.09) years for females and 77.49(SD,5.41) for males. There were 8,614 female and 9,066 male deaths during the observation period and the overall mortality rate was 73 and 80 per 1000 person years for females and males respectively. Mean duration of diabetes was 8.48(SD,7.84) years for females and 9.09 (SD,8.23) years for males.

(Table 1 about here)

Baseline mean HbA1c 2003-2006 was 7.23% (56mmol/mol)(SD,1.14) for females and 7.22%(55mmol/mol)(SD,1.09) for males (Table 2). The distribution of HbA1c was similar for females and males, a fifth had an HbA1c ≥8.0%(64mmol/mol). Fewer people had HbA1c <6.0%(42mmol/mol) for the total exposure mean compared to the baseline mean HbA1c 2003-2006(8.7% vs.12.4%). The mean baseline (2003-2006) instability metric was 43(SD,25) for females and 44(SD,24) for males. The proportion of people with a metric >80 (0-100) was around 6% for the baseline period 2003-2006 and 4% for total exposure. Not all cases had assessable HbA1c values, 5.8% (n=3,186) for total exposure.

(Table 2. About here)

Survival by HbA1c (baseline 2003-2006, total exposure) categories and glycaemic instability (for people with a diabetes duration >5 years) by gender are presented in Table 3. The HbA1c categories

indicate that survival reduces incrementally with HbA1c values  $>8\%$  (64mmol/mol); with a reduction also occurring with values  $<6\%$  (42mmol/mol). Survival is inversely associated with the instability metric for females and males and is strongest for total exposure.

(Table 3 about here)

The adjusted hazard ratios by HbA1c level for all-cause mortality (time to death) from the three Cox regression models are shown in Figure 1 for people aged 70 and over and in Appendices 1 and 2 by age-group. The data show a 'J' shaped distribution in both males and females, mortality risk increases significantly with HbA1c values  $>8\%$  (64mmol/mol) and  $<6\%$  (42mmol/mol), with some variation between models and genders. The hazard ratio for HbA1c  $<6\%$  (42mmol/mol) was 6% (Model I) and 15% (Model II) higher than the reference range for females and 4% lower (Model I) and 22% (Model II) higher for males. Conversely in the time varying model III (short-term effects) the hazard ratios were 19% and 25% lower for females and males respectively, when HbA1c was  $<6\%$  (42mmol/mol). This reduction in risk appeared to be related to the addition of polypharmacy (excluding diabetes therapies) to the time varying model (Female HR 1.08 to 0.94; Male HR 1.02 to 0.88).

(figure 1 about here)

The addition of the instability metric into the model for people with diabetes duration  $\geq 5$  years had a softening effect on the impact of higher glycaemic thresholds, extending the point at which significantly elevated hazard is observed to a HbA1c of around 10% (86mmol/mol) in females and 9.5% (80mmol/mol) in males. The risk at the lower threshold (HbA1c 6.0%, 42mmol/mol) was more exaggerated in both females and males (Figure 2, data in Appendices 3 and 4) in model II with hazard ratios of 25% and 30% higher than the reference level (7.0%–7.5%) respectively. In males, a significant excess risk was apparent for HbA1c levels  $<7.0\%$  (53mmol/mol). These risk differences were smaller in model I with hazard ratios of 9% and 11% for females and males respectively.

(figure 2 about here)

Survival diminished markedly with increasing instability in both genders, although this effect was stronger in model II than model I (Figure 3, data in Appendices 3 and 4). The hazard ratios comparing instability metric group  $>80$ –100 with 0–20 in models I–III were 1.51, 2.47 and 1.87 respectively for females and 1.57, 2.21 and 1.54 for males.

(figure 3 about here)

When the positive and negative direction metrics were added to model II people with scores outside the stable range (–20 to 20) observed reduced survival, with a greater reduction amongst people with negative rather than positive changes in HbA1c (hazard ratio: females 2.47 vs. 1.82; males 2.43 vs. 1.57) (data in Appendix 5). A cross-tabulation of the instability and direction metric (data in Appendix 6) shows a higher preponderance of negative rather than positive change for instability  $\geq 41$  in females and to a lesser degree in males. The mortality hazard observed for our other measure of variability, standard deviation of mean HbA1c, revealed a similar pattern with survival reduced for people observing a negative or positive change of 0.2% or more per annum (data in Appendices 7 and 8), with people experiencing negative change most at risk.

The findings remained similar when the comorbidity metrics were replaced in models I–III by individual comorbidities with most HbA1c level and instability parameter estimates (70%) within  $\pm 0.03$  of each other (Appendices 1–4). The removal of people with HbA1c  $<5.5\%$  (56mmol/mol) attenuated the risk associated with HbA1c  $<6\%$  (42mmol/mol) (reducing hazard ratios from 1.15 to 1.09 for females and



1.22 to 1.19 for males in Model II) with risk for all other HbA1c groups unaltered. The association between BMI and HbA1c (total exposure) was weak (female  $r=0.10$ ; males  $r=0.08$ ). Females with BMI  $<18$  were more likely to have total exposure HbA1c  $<6\%$  (42mmol/mol) than those with a BMI of 20 to  $<25$  (22.8%,  $n=74$  vs. 12.0%,  $n=701$ ). The corresponding findings for males were similar (22.1%,  $n=19$  vs. 10.7%,  $n=591$ ). Age at diagnosis had a marginal impact on survival, an instability metric of  $>61$ , placed males diagnosed  $<65$  years at greater risk than those diagnosed later whilst the reverse was apparent for females (data in Appendices 9 and 10).

The two variables associated with non-proportionality ( $p<.001$ ) were antibiotics and polypharmacy. odds ratio for HbA1c level and instability from the proportional and non-proportional hazard models were not dissimilar and risk profiles with increasing HbA1c and instability remained consistent.

## DISCUSSION

This study provides new insights into the relationship between glycaemic control and survival in older people with diabetes. This is the first analysis to consider the relationship between clinically significant variations in glycaemic control and mortality in older people. While previous studies have shown that variability in HbA1c increases hazard for diabetes complications and mortality,<sup>11,18,19</sup> these studies were not specific to older people and used variability estimations based on standard deviation(SD) of the mean HbA1c. Whereas our variability metric was weighted for clinically significant change in HbA1c ( $\geq 0.5\%$ , 5.5 mmol/mol) and we also considered the frequency and direction of variation to provide more granularity in our interpretation.

The data showed that in an older population, the frequency of clinically significant changes in HbA1c has a monotonically increasing association with mortality hazard, with that hazard being 60% greater in those with the highest instability compared to the lowest. This estimation is more modest than that reported in a recent meta-analysis of 5 studies ( $n=18,940$  patients with type 2 diabetes) which estimated a relative risk for mortality of 2.89(95% CI, 1.45–5.74) with increased glycaemia variability. However, most of the studies in this meta-analysis were more congruent with our data with mortality risk estimations ranging from 30-99%. Another difference between the previous studies and ours was that their variability measures were based on the standard deviation(SD) of HbA1c. When we considered SD in HbA1c as an alternative assessment for variation in our sensitivity analysis it was concordant with our metric. In terms of the direction of the observed variability both increases and decreases heightened risk, although the risk seems to be greater in the direction of intensification. Adding variability to our models for glycaemic control softened the risk profile with each graduated threshold of HbA1c above 6.5%(48mmol/mol) in women and at around 7%(53mmol/mol) in males, although the hazard was unaltered at the lower thresholds.

While the pathophysiological mechanisms that might explain these findings remain unknown, it is likely that any explanation is multi-factorial. It has been suggested that glycaemic variability may be explained by fluctuations in glucose control overtime but with an aggregate of hyperglycaemia driving tissue damage.<sup>20</sup> Short-term glucose variations have been postulated as a risk factor for vascular complications but this hypothesis is unproven, although a recent post-hoc analysis of an insulin trial, considered the impact of variability in fasting glucose and identified a 40% increased mortality hazard between the lowest and highest variability groups in their pooled analysis ( $n=7,586$ ).<sup>21</sup> However, in the older population, it may also be that the physiological changes that accompany older age, together with altered

nutrition and activity, are key drivers. Further work is mandated to explicate the mechanisms that drive glycaemic variation.

From a clinical perspective, these observations suggest that glycaemic stability may be an important indicator and possibly a risk predictor in older people. While these data suggest the need for caution in intensifying glycaemic control too aggressively in older people, we must consider that there may be other factors that influence glycaemic variability that independently confer hazard. In a post-hoc analysis of the ADVANCE study exploring glycaemic variation, there was elevated mortality risk in relation to higher variability in HbA1c in both the intensive and control arms of the study,<sup>22</sup> suggesting that variability was associated with mortality independent of glucose intensification. We also know from long-term follow-up of the major glycaemic intensification studies indicate an enduring survival advantage in the intensive study arms,<sup>23</sup> although another recent follow-up study or a large intensification trial did not observe any survival advantage.<sup>24</sup> Furthermore, in our data we observed limited hazard in relation to glucose lowering therapies, which would be counter to the excess intensification explanation, with only SUs and insulin being associated with modest elevated mortality risk. Huang et al<sup>3</sup> found that the patients in their lower glycaemic group had significantly less exposure to hypoglycaemic agents than those with more elevated levels of glycaemic control. Hence, it would seem unlikely that this observation can be attributed solely to excess glucose lowering, in the older population it may be that other factors such as frailty and malnutrition<sup>25</sup> or hypoglycaemia<sup>26</sup> are also important.

In terms of glycaemic control and mortality, our data concur with previous studies reporting a 'J' shaped distribution for mortality hazard.<sup>2,3,4</sup> However, our study has provided more specific estimations in relation to this distribution by: using finer level HbA1c increments (0.5%, 5.5mmol/mol) with 5 year age bands (extending to those >85 years); considering gender differences; and adjusting for the effect of low HbA1c values (<5.5%, 37mmol/mol) in our sensitivity analysis. In our model the J-shaped distribution for mortality and glycaemic control was only significant in HbA1c values <6% in both males and females, whilst there was an incremental elevation in hazard with HbA1c values >8% (64mmol/mol) in males and 8.5% (69mmol/mol) in females. These observations are partially congruent with a more recent observational study of 1279 adults aged >65 years, which reported significantly elevations in hazard with HbA1c >8% but interestingly no J-shaped distribution was noted.<sup>27</sup> Therefore, the range for glycaemic control with lower hazard may be broader than suggested by earlier analyses<sup>2,3</sup> and the risk in the lower range less marked, with the risk margins being further attenuated when the effect of glycaemic variability is added to the model.

Our findings indicate that we may need to re-evaluate how we interpret low HbA1c values in older people with diabetes. Exceptionally low HbA1c levels have previously been linked to mortality. Paprot et al<sup>13</sup> analysed data on patients with diabetes (n=6,299) over an 11 year period and found a 70% increased risk of mortality in diabetes subjects with HbA1c ≤5% (31mmol/mol), compared with a reference group of HbA1c, 5(31mmol/mol)-5.7%(39mmol/mol). Low HbA1c levels have been associated with increased inflammatory activity and altered liver function,<sup>12</sup> and in an older population this may be linked to the physical and metabolic decline observed in frailty.<sup>12</sup> Indeed, a recent prospective study has reported that frailty risk in diabetes also follows a J-shaped distribution with HbA1c, with the risk of frailty increasing when HbA1c <7.5%(58mmol/mol).<sup>27</sup> While we had no direct measure for frailty in our study, we did consider BMI as a proxy measure and although we found no correlation between low BMI and low HbA1c, we did observe a significantly elevated mortality hazard in those with a BMI ≤20. Overall, our data suggest that lower HbA1c values in older people are more likely to be a marker for elevated risk of mortality, rather than a consequence of excess glucose intensification.

While our data broadly support the targets identified in current guidelines for diabetes in older people,<sup>9,10,28,29</sup> they also suggest that some of the factors used in these guidelines for indicating the need for less stringent glycaemic control do not adequately reflect the complex interaction between ageing and the exposures that follow a diagnosis of diabetes. Furthermore, while these guidelines promote individual targets there remains an emphasis on fixed glycaemic targets to moderate therapy, rather than managing or reducing the exposure to glycaemic variability. Our analysis suggests that in older people glycaemic change and variability independent of therapeutic intervention should be considered in clinical risk assessment and management. Perhaps, guidelines should encourage clinicians to be more attentive to both a declining or a rising HbA1c, with an emphasis on gradual intensification and glycaemic stability.

We recognise some important limitations to our study. As with all studies utilising large data sets of routinely collected data there can be some variation in the accuracy of data, although the data concord with other UK national datasets.<sup>14</sup> We were also limited by not having any specific data on important indicators such as frailty, this may be remedied in future UK studies as the new contract for general practice includes frailty screening for those aged >65 years. In addition, we did not characterise diabetes Type as this is notoriously challenging in primary care data, a reasonable estimation would be that 90% of subjects were Type 2. It is also important to emphasise that we did not have access to blood glucose measurements that would reflect glucose variability as these are not recorded in primary care. Therefore, we could not explore the relationship between glycaemic and glucose variability, which may be important in the context of the study population. Furthermore, the glycaemic data (HbA1c) were not collected in a controlled time specified way, a more regulated framework of data collection would have reduced potential measurement bias. Finally, as an observational study our interpretation is restricted to inferential association and not causality.

In conclusion, this analysis suggests that glycaemic variability may be an important factor in understanding mortality hazard in this population, affirming the need to develop better strategies for glucose management in older people. While developing a more stable glycaemic environment for older people may be important, further examination of the relationship between glycaemic variability and clinical outcomes is required to inform appropriate levels and models for glycaemic control in this population. This may enable the determination of dynamic, risk modelled and individualised targets for older people rather than fixed thresholds, that may also reflect gender differences. Our study also suggests that we need to reconsider how we evaluate the J-shaped curve observed in the relationship between HbA1c thresholds and mortality, suggesting that mortality at the lower end of this distribution may be related to age related phenomena rather than excess glycaemic intensification.

## Contributors

AF, led on the study design and the analytical interpretation of the study findings, he also contributed to data assessment and statistical interpretation. TM, was the statistician on the study and led on the data-management and statistical analysis for the study, he also co-ordinated the necessary approvals and licensing of the dataset. HM contributed to the analytical interpretation of the data. AJS, gave oversight into the study design, context and analytical interpretation of the data.

## Conflicts of Interests

All authors declare no competing interests. AF has in the past received honoraria or unrestricted educational grants unrelated to this study from the following companies: Ascensia Diabetes Care; Abbott; Roche; and Eli Lilly. AJS has in the past received honoraria or unrestricted educational grants unrelated to this study from the following companies: MSD, Pfizer, Takeda, Sanofi and Eli Lilly.

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## FIGURE LEGENDS

**Figure 1: Adjusted hazard ratios (95% CI) by HbA1c level for all-cause mortality: Females and Males.**

**Legend:** Model I (Baseline mean 2003-2006) is indicated in red; Model II (Total exposure mean) is indicated in blue; and Model III (Updated cumulative (time varying) mean) is indicated in Red.

**Figure 2: Adjusted hazard ratios (95% CI), with instability metric included in the model, by HbA1c**

**level for all-cause mortality: Females and Males, diabetes duration  $\geq 5$  years. Legend:** Model I (Baseline mean 2003-2006) is indicated in red; Model II (Total exposure mean) is indicated in blue; Model III (Updated cumulative (time varying) mean) is indicated in Red; and the dotted line indicates total exposure mean without instability.

**Figure 3: Adjusted hazard ratios (95% CI) by instability level for all-cause mortality: Females and Males,**

**diabetes duration  $\geq 5$  years. Legend:** Model I (Baseline mean 2003-2006) is indicated in red; Model II (Total exposure mean) is indicated in blue; and Model III (Updated cumulative (time varying) mean) is indicated in Red.

